REMARKS

The Office Action mailed December 28, 2001 has been received and carefully reviewed.

After entry of the present amendment, claims 1-3, 5, 6, 9, 10 and 16-21 are pending in the application. Claims 4, 7, 8 and 11-15 were cancelled without prejudice. Claims 1, 5 and 16 have been amended and new claims 19-21 have been added. Favorable reconsideration and withdrawal of the rejections of the claims is respectfully requested in light of the amendments and comments presented herein.

No new matter is introduced. Applicants submit that the amended and newly presented claims are supported by the specification. In particular, new claims 19-21 were added to replace originally filed claims 11-15, but are drafted in appropriate method format using active steps instead of the "use" format previously presented.

For the reasons provided herein, Applicants respectfully submit the amended and newly presented claims are in condition for allowance, and notification to that effect is earnestly solicited.

Rejection of Claims Under § 112, First Paragraph

In the Office Action, claims 1-18 were rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse these rejections, both as applied to the claims previously presented and inasmuch as they may be applied to the newly presented claims.

In the Office Action, it is asserted that the claims were not enabled by the specification for the following reasons: 1) the specification does not provide enablement for any cell type to be used in the polysaccharide matrix for repairing a damaged myocardium; 2) the specification does not provide enablement as to the type, mechanism or level of soluble factors to be released by the microspheres; 3) the specification does not address the issue of transplant rejection and graft-versus-host disease; 4) the specification does not address the issue of appropriate sizing of the graft; and 5) the specification does not address the prevention of the activation of the coagulation system. These rejections are addressed in turn below.

Any Cell Type

Applicants do not agree that one of skill in the art would not be able to adapt the present invention to all equivalent cell types. However, to further prosecution of the application, amended claims 1 and 16 and new claim 19 each includes a recitation of a Markush grouping of specific cell types mentioned and exemplified in the instant specification.

The specification teaches how to create the graft of the invention using fetal cardiomyoctes (see page 10, Example 1), cardiofibroblasts (see page 11, Example 1) and endothelial cells (see pages 11-13, Examples 1 and 2). Thus, the specification teaches three cell types from which the graft may be formed. Based on these teachings, one of skill in the art would be able to adapt the invention to any of the cell types recited. The use of embryonic stem cells, which are totipotent and by definition possess the ability to differentiate into a variety of cell types, are especially adaptable for use in the present invention.

Soluble Factors

Applicants do not agree that one of skill in the art would not be able to adapt the present invention to use polymeric microspheres to release any soluble factor into the graft. However, to further prosecution of the application, claims 1 and 16 recite "microspheres capable of releasing soluble growth factors" and claims 7 and 8, which recited "controlled-release polymeric microspheres, said microspheres being able of releasing soluble factors in a controlled manner " and "soluble growth factors, genes or DNA," respectively, were cancelled herein. New claim 19, which is directed to a method of preparing a tissue-engineered biograft, also recites "microspheres capable of releasing soluble growth factors" and is therefore believed to be fully enabled by the instant specification. See Example 3, pages 15-16.

Transplant Rejection and GVHD

As is acknowledged in the Office Action, the issues of transplant rejection and graft-versus-host disease are well known in the art. Thus, it is respectfully asserted that one of skill in the art would be fully aware of, and capable of effectively using,

immunosuppressive agents to prevent rejection, as well as the need for transplanting only xenocompatible tissue and cells.

The Office Action asserts that "the specification reads on the installation of xenogeneic or allogenic cells into a mammal." This is incorrect with respect to xenogeneic cells. The specification, including the working examples therein, clearly demonstrates the invention is intended to be used in a manner that would prevent rejection. The specification describes culturing fetal and neonatal cardiomyocytes from rats (see page 10, lines 20-25) with 3D scaffolds to produce a biograft that is then transplanted in rats (see page 16, example 4). Thus, there is a clear recognition in the specification, as well as in the art, that allogeneic and syngeneic cells would be suitable for use in the invention. In addition, the specification clearly describes successful transplantation of an engineered matrix according to the invention using allogeneic cells.

Sizing

Applicants respectfully assert that the selection of an appropriate graft size is well within the capability of one skilled in the art. Graft size is determined by surgeons as a matter of routine based on parameters known in the art of transplantation. Sizing will depend on the state of the disease, the age of the patient, and additional parameters that are well within the skill of a surgeon in the art performing graft transplantation and need not be taught *de novo* in the instant specification to enable such skilled surgeons to use the invention.

Prevention of thrombosis

Applicants point out that the alginates used in the invention are non-thrombogenic. Therefore, the prevention of activation of the coagulation system is not relevant to the present invention.

Conclusion

In conclusion, based on the foregoing, it is believed that the claims as presented are fully enabled by the specification. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112, Second Paragraph

In the Office Action, claims 11-15 were rejected under 35 U.S.C. § 112, second paragraph. These claims have been cancelled in the present amendment. The substance of these claims is presented in appropriate method format in new claims 19-21, which are believed to fully comply with 35 U.S.C. § 112, second paragraph. Accordingly, withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 102(b)

In the Office Action, claims 11-17 were rejected under 35 U.S.C. § 102(b) as anticipated by Shapiro et al. (WO 97/44070).

Claims 11-15 have been cancelled herein. However, new claims 19-21 recite the subject matter of claims 11-15. Therefore, Applicants request consideration of the arguments presented herein inasmuch as they may be applied to these claims.

Shapiro et al. teach a method for preparing polysaccharide sponges and their use as matrices, supports or scaffolds for implantation into a patient. See page 1. However, Shapiro et al. do not teach the preparation or use of a polysaccharide matrix comprising controlled release polymeric microspheres capable of releasing soluble growth factors. Amended claim 16 and new claim 19 now recite this aspect of the present invention, thereby overcoming the rejection.

Accordingly, it is respectfully requested that the rejection of claims under 35 U.S.C. § 102(b) be withdrawn.

Rejections Under 35 U.S.C. § 102(a)

In the Office Action, claims 1-4, 9 and 11-18 are rejected over Leor et al. (European Heart Journal, vol. 20, p.29 (1999)).

Claims 11-15 have been cancelled herein. However, new claims 19-21 recite the subject matter of claims 11-15. Therefore, Applicants request consideration of the arguments presented herein inasmuch as they may be applied to these claims.

Although Applicants do not concede the correctness of the rejection, claim 1 has been amended to recite a polysaccharide matrix that comprises controlled-release polymeric microspheres, said microspheres being capable of releasing soluble growth factors in a controlled manner. This aspect of the invention is not disclosed by Leor et al. Claim 1 as amended, and claims 2-4 and 9 which depend from claim 1, are therefore not anticipated. Claim 16 (and claims 17 and 18 depending therefrom) and new claim 19 (and the new claims depending therefrom) also includes the recitation of microspheres capable of releasing soluble growth factors and are similarly not anticipated.

Accordingly, it is respectfully requested that the rejection of claims under 35 U.S.C. § 102(a) be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

In the Office Action, claims 1-4, 7 and 8 are rejected under 35 U.S.C. § 103(a) over the combination of Mickle et al. (U.S. Pat. No. 6,099,832), Osiris therapeutics (WO 99/03973), Shapiro et al. (WO 97/44070) and Cohen et al. (U.S. Pat. No. 5,494,862).

To establish a prima facie case of obviousness, three criteria must be met: 1) there must be some suggestion or motivation to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the combined references must teach all of the claimed limitations. MPEP § 2143. In addition, "the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention." MPEP § 2141. Here, Applicants respectfully assert that not only is there no reasonable expectation of success afforded by any of the references, but also that the rejection was made using impermissible hindsight.

Mickle et al. describe the use of several cell types in forming a graft, but do not teach the use of a polysaccharide matrix.

Shapiro et al. describe a bioerodible polysaccharide matrix made from alginate, but do not teach a method of repairing a damaged myocardium. Shapiro et al. do not suggest that one using the polysaccharide matrix would have a reasonable expectation of success for this application. Shapiro et al. do not teach any of the recited cell types for co-culturing with matrix to provide a tissue-engineered biograft. Thus, one of skill in the

art would not be motivated to combine Shapiro with Mickle, despite the teaching in Shapiro that polysaccharide matrices are widely available and of relatively low cost.

Osiris therapeutics teach a method for producing cardiomyocytes *in vivo* using mesenchymal stem cells and also teach administering MSCs in a biocompatible medium which may solidify at the site of myocardial damage into a scaffolding. This is not the present invention, even in combination with Mickle. Alternatively, Osiris therapeutics teach administering MSCs in a solid matrix that is implanted in its final form. This is also not the present invention. Osiris therapeutics fails to mention the requirement of growing the cells in the matrix *in vitro* until a contracting tissue biograft is formed prior to transplantation, as in the present invention. Osiris therapeutics does not mention a polysaccharide, much less an alginate matrix. Thus, one of skill in the art would not be successful in arriving at the present invention by combining Osiris therapeutics with Mickle.

The polymer matrix of Cohen is much different from that of the present invention. Cohen et al. teach incorporating biological material into the polymer matrix while it remains hydrated to create a wet hydrogel. In contrast, the polysaccharide matrix comprising microspheres of the present invention create a dry scaffold with a pore size in the micron to hundred micron size range with a high degree of pore interconnectivity. Thus, the matrix of the present invention is able to support the reorganization of cells into three-dimensional tissue, allows for better mass transport and oxygen diffusion, and is capable of becoming vascularized after transplantation. One of skill in the art, armed with Cohen, would not reasonably expect success in creating the present invention, even if they were to combine Cohen with the other cited references.

Based on the foregoing, it is clear that one of skill in the art would not have any reasonable expectation of success in combining the four cited references. None of the references provide any suggestion that a combination would be successful. Thus, the combination can only be based on impermissible hindsight, using the present specification as a template. For these reasons, it is respectfully requested that the rejection of the claims based on 35 U.S.C. § 103(a) be withdrawn.

Summary

In summary, Applicants believe that each of claims 1-3, 5, 6, 9, 10 and 16-21 are in condition for allowance. Further and favorable action in the form of a Notice of Allowance is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below, if the Examiner believes that doing so will expedite prosecution of this patent application.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 4, 7, 8 and 11-15 were cancelled. Claims 1, 5 and 16 have been amended as follows:

1. (AMENDED) A method for repairing a damaged myocardium in a mammal, comprising:

a) providing a three-dimensional porous polysaccharide matrix;

b) introducing mammalian cells into said matrix;

c) growing said cells in said matrix *in vitro*, until a tissue-engineered biograft is formed, comprising a contracting tissue; and

d) transplanting the tissue-engineered biograft onto the myocardial tissue or myocardial scar tissue of said mammal, optionally previously removing scar or dead tissue from the site of implantation;

wherein the mammalian cells are selected from the group consisting of fetal cardiomyocytes, neonatal cardiomyocytes, adult cardiac cells, fibroblasts, smooth muscle cells, endothelial cells, skeletal myoblasts, mesenchymal stem cells and embryonic stem cells; and

wherein said polysaccharide matrix further comprises controlled-release polymeric microspheres, said microspheres being capable of releasing soluble growth factors in a controlled manner.

5. (AMENDED) A method according to claim [4] 3, wherein the mammalian cells comprise:

a) fetal cardiomyocytes or neonatal cardiomyocytes or mixtures thereof [are]; and

b) [co-cultured with] endothelial cells, cardiofibroblasts or smooth muscle cells or mixtures thereof.

16. (AMENDED) A tissue-engineered cardiac biograft for transplantation into myocardial tissue or myocardial scar tissue, comprising:

a porous polysaccharide matrix [containing] comprising controlled-release polymeric microspheres capable of releasing soluble growth factors; and

mammalian cells[,]selected from the group consisting of fetal cardiomyocytes, neonatal cardiomyocytes, adult cardiac cells, fibroblasts, smooth muscle cells, endothelial cells, skeletal myoblasts, mesenchymal stem cells and embryonic stem cells;

wherein said cells have been cultured in said matrix *in vitro*.

Claims 19-21 are new.

19. (NEW) A method of preparing a three-dimensional tissue-engineered biograft comprising:

a) providing a porous polysaccharide matrix comprising microspheres capable of releasing soluble growth factors; and

b) co-culturing the porous polysaccharide matrix *in vitro* with mammalian cells selected from the group consisting of fetal caridomyocytes, neonatal cardiomyocytes, adult cardiac cells, fibroblasts, smooth muscle cells, endothelial cells, skeletal myoblasts, mesenchymal stem cells and embryonic stem cells, until a cardiac-like tissue is formed, comprising a tissue-engineered biograft.

20. (NEW) The method of claim 19, wherein the porous polysaccharide matrix comprises an alginate polysaccharide.

21. (NEW) The method of claim 19, wherein the porous polysaccharide matrix generates a scaffold.